



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-613

Food and Drug Administration.
Rockville MD 20857

NDA 13-400/S-085

NOV 10 1998

Merck Research Laboratories
Attention: Jeffery R. White, M.D.
PO Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug application dated April 9, 1998, received April 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aldomet (methyldopa) Tablets.

We acknowledge receipt of your submission dated October 1, 1998.

This supplemental new drug application provides for final printed labeling revised under **PRECAUTIONS: Drug Interactions** to add a statement describing a drug interaction between methyldopa and ferrous sulfate or ferrous gluconate. In addition, all reference to Aldomet Oral Suspension were deleted from the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 6, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



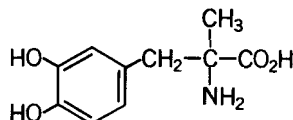
MERCK & CO., INC.
West Point, PA 19486, USA

TABLETS

ALDOMET (METHYLDOPA)

DESCRIPTION

ALDOMET (Methyldopa) is an antihypertensive drug. Methyldopa, the L-isomer of alpha-methyldopa, is levo-3-(3,4-dihydroxyphenyl)-2-methylalanine. Its empirical formula is $C_{10}H_{13}NO_4$, with a molecular weight of 211.22, and its structural formula is:



Methyldopa is a white to yellowish white, odorless fine powder, and is soluble in water.

ALDOMET is supplied as tablets, for oral use, in three strengths: 125 mg, 250 mg, or 500 mg of methyldopa per tablet. Inactive ingredients in the tablets are: calcium disodium edetate, cellulose, citric acid, colloidal silicon dioxide, D&C Yellow 10, ethylcellulose, guar gum, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, propylene glycol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

ALDOMET is an aromatic-amino-acid decarboxylase inhibitor in animals and in man. Although the mechanism of action has yet to be conclusively demonstrated, the antihypertensive effect of methyldopa probably is due to its metabolism to alpha-methylnorepinephrine, which then lowers arterial pressure by stimulation of central inhibitory alpha-adrenergic receptors, false neurotransmission, and/or reduction of plasma renin activity. Methyldopa has been shown to cause a net reduction in the tissue concentration of serotonin, dopamine, norepinephrine, and epinephrine.

Only methyldopa, the L-isomer of alpha-methyldopa, has the ability to inhibit dopa decarboxylase and to deplete animal tissues of norepinephrine. In man the antihypertensive activity appears to be due solely to the L-isomer. About twice the dose of the racemate (DL-alpha-methyldopa) is required for equal antihypertensive effect.

Methyldopa has no direct effect on cardiac function and usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. Cardiac output usually is maintained without cardiac acceleration. In some patients the heart rate is slowed.

Normal or elevated plasma renin activity may decrease in the course of methyldopa therapy.

ALDOMET reduces both supine and standing blood pressure. Methyldopa usually produces highly effective lowering of the supine pressure with infrequent symptomatic postural hypotension. Exercise hypotension and diurnal blood pressure variations rarely occur.

Pharmacokinetics and Metabolism

The maximum decrease in blood pressure occurs four to six hours after oral dosage. Once an effective dosage level is attained, a smooth blood pressure response occurs in most patients in 12 to 24 hours. After withdrawal, blood pressure usually returns to pretreatment levels within 24-48 hours.

Methyldopa is extensively metabolized. The known urinary metabolites are: a-methyldopa mono-O-sulfate; 3-O-methyl-a-methyldopa; 3,4-dihydroxyphenylacetone; a-methyldopamine; 3-O-methyl-a-methyldopamine and their conjugates.

Approximately 70% of the drug which is absorbed is excreted in the urine as methyldopa and its mono-O-sulfate conjugate. The renal clearance is about 130 mL/min in normal subjects and is diminished in renal insufficiency. The plasma half-life of methyldopa is 105 minutes. After oral doses, excretion is essentially complete in 36 hours.

Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

INDICATION AND USAGE

Hypertension.

CONTRAINDICATIONS

ALDOMET is contraindicated in patients:

- with active hepatic disease, such as acute hepatitis and active cirrhosis
- with liver disorders previously associated with methyldopa therapy (see WARNINGS)
- with hypersensitivity to any component of these products.
- on therapy with monoamine oxidase (MAO) inhibitors.

WARNINGS

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10 to 20 percent of patients develop a positive direct Coombs test which usually occurs between 6 and 12 months of methyldopa therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia.

Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, the physician should determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

Before treatment is started, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy.

If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted.

When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Occasionally, fever has occurred within the first 3 weeks of methyldopa therapy, associated in some cases with eosinophilia or abnormalities in one or more liverfunctiontests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, and prothrombin time. Jaundice, with or without fever, may occur with onset usually within the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. In others the findings are consistent with hepatitis and hepatocellular injury.

Rarely, fatal hepatic necrosis has been reported after use of methyldopa. These hepatic changes may represent hypersensitivity reactions. Periodic determinations of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with a primary effect on the granulocytes has been seen. The granulocyte count returned promptly to normal on discontinuance of the drug. Rare cases of granulocytopenia have been reported. In each instance, upon stopping the drug, the white cell count returned to normal. Reversible thrombocytopenia has occurred rarely.

PRECAUTIONS

General

Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction (see WARNINGS).

Some patients taking methyldopa experience clinical edema or weight gain which may be controlled by use of a diuretic. Methyldopa should not be continued if edema progresses or signs of heart failure appear.

Hypertension has recurred occasionally after dialysis in patients given methyldopa because the drug is removed by this procedure.

Rarely involuntary choreoathetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, stop therapy.

Laboratory Tests

Blood count, Coombs test, and liver function tests are recommended before initiating therapy and at periodic intervals (see WARNINGS).

Drug Interactions

When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Patients may require reduced doses of anesthetics when on methyldopa. If hypotension does occur during anesthesia, it

usually can be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

When methyldopa and lithium are given concomitantly the patients should be carefully monitored for symptoms of lithium toxicity. Read the circular for lithium preparations.

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulfate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa. Coadministration of methyldopa with ferrous sulfate or ferrous gluconate is not recommended.

Monoamine oxidase (MAO) inhibitors: See CONTRAINDICATIONS.

Drug/Laboratory Test Interactions

Methyldopa may interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Interference with spectrophotometric methods for SGOT analysis has not been reported.

Since methyldopa causes fluorescence in urine samples at the same wave lengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa does not interfere with measurement of VMA (vanillylmandelic acid), a test for pheochromocytoma, by those methods which convert VMA to vanillin. Methyldopa is not recommended for the treatment of patients with pheochromocytoma. Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was seen when methyldopa was given for two years to mice at doses up to 1800 mg/kg/day or to rats at doses up to 240 mg/kg/day (30 and 4 times the maximum recommended human dose in mice and rats, respectively, when compared on the basis of body weight; 2.5 and 0.6 times the maximum recommended human dose in mice and rats, respectively, when compared on the basis of body surface area; calculations assume a patient weight of 50 kg).

Methyldopa was not mutagenic in the Ames Test and did not increase chromosomal aberration or sister chromatid exchanges in Chinese hamster ovary cells. These *in vitro* studies were carried out both with and without exogenous metabolic activation.

Fertility was unaffected when methyldopa was given to male and female rats at 100 mg/kg/day (1.7 times the maximum daily human dose when compared on the basis of body weight; 0.2 times the maximum daily human dose when compared on the basis of body surface area). Methyldopa decreased sperm count, sperm motility, the number of late spermatids and the male fertility index when given to male rats at 200 and 400 mg/kg/day (3.3 and 6.7 times the maximum daily human dose when compared on the basis of body weight; 0.5 and 1 times the maximum daily human dose when compared on the basis of body surface area).

Pregnancy

Pregnancy Category B. Reproduction studies performed with methyldopa at oral doses up to 1000 mg/kg in mice, 200 mg/kg in rabbits and 100 mg/kg in rats revealed no evidence of harm to the fetus. These doses are 16.6 times, 3.3 times and 1.7 times, respectively, the maximum daily human dose when compared on the basis of body weight; 1.4 times, 1.1 times and 0.2 times, respectively, when compared on the basis of body surface area; calculations assume a patient weight of 50 kg. There are, however, no adequate and well-controlled studies in pregnant women in the first trimester of pregnancy. Because animal reproduction studies are not always predictive of human response, ALDOMET should be used during pregnancy only if clearly needed.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of fetal harm appears remote. In five studies, three of which were controlled, involving 332 pregnant hypertensive women, treatment with ALDOMET was associated with an improved fetal outcome. The majority of these women were in the third trimester when methyldopa therapy was begun.

In one study, women who had begun methyldopa treatment between weeks 16 and 20 of pregnancy gave birth to infants whose average head circumference was reduced by a small amount (34.2 ± 1.7 cm vs. 34.6 ± 1.3 cm [mean \pm 1 S.D.]). Long-term follow up of 195 (97.5%) of the children born to methyldopa-treated pregnant women (including those who began treatment between weeks 16 and 20) failed to uncover any significant adverse effect on the children. At four years of age, the developmental delay commonly seen in children born to hypertensive mothers was less evident in those whose mothers were treated with methyldopa during pregnancy than those whose mothers were untreated. The children of the treated group scored consistently higher than the children of the untreated group on five major indices of intellectual and motor development. At age seven and one-half developmental scores and intelligence indices showed no significant differences in children of treated or untreated hypertensive women.

TABLETS ALDOMET (METHYLDOPA)

Circular Number 7843431



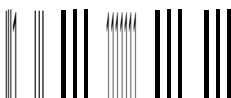
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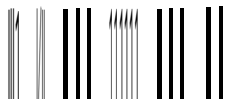
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Nursing Mothers

Methyldopa appears in breast milk. Therefore, caution should be exercised when methyldopa is given to a nursing woman.

Pediatric Use

There are no well-controlled clinical trials in pediatric patients. Information on dosing in pediatric patients is supported by evidence from published literature regarding the treatment of hypertension in pediatric patients. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms. However, significant adverse effects due to ALDOMET have been infrequent and this agent usually is well tolerated.

The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity.

Cardiovascular: Aggravation of angina pectoris, congestive heart failure, prolonged carotid sinus hypersensitivity, orthostatic hypotension (decrease daily dosage), edema or weight gain, bradycardia.

Digestive: Pancreatitis, colitis, vomiting, diarrhea, sialadenitis, sore or "black" tongue, nausea, constipation, distension, flatulence, dryness of mouth.

Endocrine: Hyperprolactinemia.

Hematologic: Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia, hemolytic anemia; positive tests for antinuclear antibody, LE cells, and rheumatoid factor, positive Coombs test.

Hepatic: Liver disorders including hepatitis, jaundice, abnormal liver function tests (see WARNINGS).

Hypersensitivity: Myocarditis, pericarditis, vasculitis, lupus-like syndrome, drug-related fever, eosinophilia.

Nervous System/Psychiatric: Parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements, symptoms of cerebrovascular insufficiency, psychic disturbances including nightmares and reversible mild psychoses or depression, headache, sedation, asthenia or weakness, dizziness, lightheadedness, paresthesias.

Metabolic: Rise in BUN.

Musculoskeletal: Arthralgia, with or without joint swelling; myalgia.

Respiratory: Nasal stuffiness.

Skin: Toxic epidermal necrolysis, rash.

Urogenital: Amenorrhea, breast enlargement, gynecomastia, lactation, impotence, decreased libido.

OVERDOSAGE

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastrointestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, lightheadedness, constipation, distention, flatulence, diarrhea, nausea, vomiting).

In the event of overdosage, symptomatic and supportive measures should be employed. When ingestion is recent, gastric lavage or emesis may reduce absorption. When ingestion has been earlier, infusions may be helpful to promote urinary excretion. Otherwise, management includes special attention to cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

Sympathomimetic drugs [e.g., levarterenol, epinephrine, ARAMINE* (Metaraminol Bitartrate)] may be indicated. Methyldopa is dialyzable.

The oral LD₅₀ of methyldopa is greater than 1.5 g/kg in both the mouse and the rat.

DOSAGE AND ADMINISTRATION**ADULTS****Initiation of Therapy**

The usual starting dosage of ALDOMET is 250 mg two or three times a day in the first 48 hours. The daily dosage then may be increased or decreased, preferably at intervals of not less than two days, until an adequate response is achieved. To minimize the sedation, start dosage increases in the evening. By adjustment of dosage, morning hypotension may be prevented without sacrificing control of afternoon blood pressure.

When methyldopa is given to patients on other antihypertensives, the dose of these agents may need to be adjusted to effect a smooth transition. When ALDOMET is given with antihypertensives other than thiazides, the initial dosage of ALDOMET should be limited to 500 mg daily in divided doses; when ALDOMET is added to a thiazide, the dosage of thiazide need not be changed.

Maintenance Therapy

The usual daily dosage of ALDOMET is 500 mg to 2 g in two to four doses. Although occasional patients have responded to higher doses, the maximum recommended daily dosage is 3 g. Once an effective dosage range is attained, a smooth blood pressure response occurs in most patients in 12 to 24 hours. Since methyldopa has a relatively short duration of action, withdrawal is followed by return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure.

Occasionally tolerance may occur, usually between the second and third month of therapy. Adding a diuretic or increasing the dosage of methyldopa frequently will restore effective control of blood pressure. A thiazide may be added at any time during methyldopa therapy and is recommended if therapy has not been started with a thiazide or if effective control of

blood pressure cannot be maintained on 2 g of methyldopa daily.

Methyldopa is largely excreted by the kidney and patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

PEDIATRIC PATIENTS

Initial dosage is based on 10 mg/kg of body weight daily in two to four doses. The daily dosage then is increased or decreased until an adequate response is achieved. The maximum dosage is 65 mg/kg or 3 g daily, whichever is less. (See PRECAUTIONS, Pediatric Use.)

HOW SUPPLIED

No. 3341-- Tablets ALDOMET, 125 mg, are yellow, film coated, round tablets, coded MSD 135 on one side and ALDOMET on the other. They are supplied as follows:

NDC 0006-0135-68 bottles of 100.

No. 3290-- Tablets ALDOMET, 250 mg, are yellow, film coated, round tablets, coded MSD 401 on one side and ALDOMET on the other. They are supplied as follows:

NDC 0006-0401-68 bottles of 100

(6505-00-890-1856, 250 mg 100's)

NDC 0006-0401-82 bottles of 1000

(6505-00-931-6646, 250 mg 1000's).

No. 3292 = Tablets ALDOMET, 500 mg, are yellow, film coated, round tablets, coded MSD 516 on one side and ALDOMET on the other. They are supplied as follows:

NDC 0006-0516-68 bottles of 100

(6505-01-003-4119, 500 mg 100's)

NDC 0006-0516-74 bottles of 500

(6505-01-199-8339, 500 mg 500's).

Storage

Store Tablets ALDOMET in a well-closed container at controlled room temperature [15-30°C (59-86°F)].



Disby:

MERCK & CO., INC., West Point, PA 19486, USA

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